

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/12113

A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : C07D 491/044, 491/10, 263/10; C07C 229/30; C07F 7/02 US CL : 548/110, 237, 406, 411, 453; 560/170 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 548/110, 237, 406, 411, 453; 560/170 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Continuation Sheet		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 2004/071382 A2 (STADLER, et al.), 26 August 2004 (26.08.2004), at p. 3, lines 26 - 29 (especially compounds labelled "Salinosporamide E" and "Salinosporamide-A"); see also individual compounds at page 7, lines 1 - 7; page 11, lines 2 - 4; and page 12, lines 1 - 4.	1 - 45
X, P --- A, P	U.S. 2004/0138196 A1 (FENICAL, et al.), 15 July 2004 (15.07.2004), at page 8, col. 2, lines 1 - 33 (Claims 1 - 6, compounds of structure (I)); [the specific compound of Claim 7, page 8, lines 34 - 37, and shown in Figure 1 is excluded from the present application by proviso].	1 - 16, 45 ----- 17 - 44
X, P	WO 2005/002572 A2 (PALLADINO, M., et al.), 13 January 2005 (13.01.2005), at p. 18, lines 3 - 6 (especially compounds II-1(b) and II-(c) and II-3 and II-4); and page 30, lines 1 - 2 (compounds II-17, II-18, and II-19).	1 - 45
A	COREY, E. and REICHARD, G., "Total Synthesis of Lactacystin," J. Amer. Chem. Soc., vol. 114(26), pages 10677-10678 (Dec. 1992), at p. 10678, especially Scheme I, compound 1.	17 - 44
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 15 August 2005 (15.08.2005)		Date of mailing of the international search report 19 OCT 2005
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-8300		Authorized officer Anthony J. Paviglianiti <i>Anthony J. Paviglianiti</i> Telephone No. (571) 272-3107

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C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	COREY, E., and WEI-DONG, Z., "An Efficient Total Synthesis of a New and Highly Active Analog of Lactacystin," Tetrahedron Letters, vol. 39(41), pages 7475-7478 (Oct. 1998), at p. 7475, lines 15 - 24 (effects of structural features of lactacystin on its activity).	1 - 16, 45
A	PANEK, J., and MASSE, C., "Total Synthesis of (+)-Lactacystin," Angew. Chem. Int. Ed., vol. 38(8) (April 1999), at p. 1094, Scheme 1 (compounds 1 and 2).	17 - 44
A	SOUCY, F., et al., "A Novel and Efficient Synthesis of a Highly Active Analogue of clasto-Lactacystin Beta-Lactone," vol. 121(43), pages 9967-9976 (Nov. 1999), at p. 9968, col. 2, lines 4 - 16, including compound 4; see also p. 9969, Scheme 2, compounds 4 and 9.	1 - 45
A	CRANE, S., and COREY, E., "A Novel Enantioselective Synthetic Route to Omuralide Analogues with the Potential for Species Selectivity in Proteasome Inhibition," vol. 3(9), pages 1395-1397 (May 2001), at p. 1395, col. 2, compounds 3 and 4; see also p. 1396, Scheme 1.	1 - 45
A	WO 02/094311 A1 (KLIMKO and HELLBERG), 28 November 2002 (28.11.2002), at p. 11, compounds 1 - 4; and p. 19, lines 11 - 12 (Claim 4).	1 - 45
A	SARAVANAN, P., and COREY, E., "A Short, Stereocontrolled, and Practical Synthesis of Alpha-Methylomuralide, a Potent Inhibitor of Proteasome Function," J. Org. Chem., vol. 68(7), pages 2760-2764 (April 4, 2003; available on Web February 20, 2003), at p. 2761, Scheme 1, compounds 3 and 13.	1 - 45

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Continuation of B. FIELDS SEARCHED Item 3:

CAS - STN Online structure search; American Chemical Society Journals; search term: salinosporamide, lactacystin, beta-lactone; proteasome.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
ERNEST V. LINEK
28 STATE STREET - 28TH FLOOR
BOSTON, MA 02109

PCT

REC'D 21 OCT 2005
WIPO PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference 004979-00050		Date of mailing (day/month/year) 19 OCT 2005
FOR FURTHER ACTION See paragraph 2 below		
International application No. PCT/US05/12113	International filing date (day/month/year) 11 April 2005 (11.04.2005)	Priority date (day/month/year) 09 April 2004 (09.04.2004)
International Patent Classification (IPC) or both national classification and IPC IPC(7): C07D 491/044, 491/10, 263/10; C07C 229/30; C07F 7/02 and US Cl.: 548/110, 237, 406, 411, 453; 560/170		
Applicant PRESIDENT AND FELLOWS OF HARVARD COLLEGE		

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

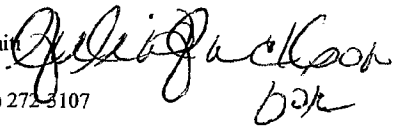
2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-8300	Authorized officer Anthony J. Pavigliani  Telephone No. (571) 272-3107
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**WRITTEN OPINION OF THE
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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>1 - 45</u>	YES
	Claims <u>NONE</u>	NO
Inventive step (IS)	Claims <u>1 - 45</u>	YES
	Claims <u>NONE</u>	NO
Industrial applicability (IA)	Claims <u>1 - 45</u>	YES
	Claims <u>NONE</u>	NO

2. Citations and explanations:

Claims 1 - 45 meet the criteria set out in PCT Article 33(2)-(3), and possess novelty and an inventive step, because the prior art does not teach or fairly suggest the compounds of Formula (Ia), Formula (IIa), or Formula (IIIa) ("salinosporamide" and "lactacystin" derivatives), as depicted in **Claims 1, 9 and 17**, respectively. In addition, the synthetic intermediates claimed in **Claims 26 - 44**, while similar to several intermediates used in making related compounds, were neither directly disclosed or fairly suggested by the prior art, and thereby possess novelty and an inventive step as well. **Claim 45**, which recites a compound that is limited by a specific stereoisomeric configuration, is not found in the prior art or fairly suggested by it, and so possesses novelty and an inventive step.

Claims 1 - 25 are free of the prior art in part because the compounds of Formula (Ia), Formula (IIa) and Formula (IIIa) require the substituent "**R**³" at the 4-position of the pyrrolidine ring to be an alkyl, alkenyl, alkynyl, cycloalkyl, etc., while the compounds disclosed in the prior art have only a hydrogen atom at that site. The difference in substitution at this site is significant for the molecule's biological activity and its stability: as noted by authors E.J. Corey and Z.L. Wei-Dong in their article in *Tetrahedron Letters*, "most of the structural features of the [lactacystin molecule] are critical to its activity...the hydroxy at C(6) must be *cis*...for proteasome inactivation...removal of the methyl substituent at [the adjacent site on the ring] strongly reduces bioactivity...and also leads to chemical instability resulting from facile elimination of the hydroxyl at [the **R**³ site]..." Corey, E., and Wei-Dong, Z., "An Efficient Total Synthesis of a New and Highly Active Analog of Lactacystin," *Tetrahedron Letters*, vol. 39(41), pages 7475-7478 (Oct. 1998), at page 7475, especially at lines 15 - 19. Thus the substitution of an alkyl, alkenyl, alkynyl, or cycloalkyl group at the **R**³ site on the pyrrolidine ring would not be anticipated or fairly suggested by compounds in the prior art which have a hydrogen atom at that site, as the stability and biological activity of the molecule would not be predictable as related to the known compounds; therefore, the claimed compounds possess novelty and an inventive step over the prior art.

Claims 1 - 45 all meet the criteria set out in PCT Article 33(4), and thus satisfy the requirement for industrial applicability, because the subject matter claimed in **Claims 1 - 45** can be made or used in industry.

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 26 - 44 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 as indefinite for the following reason(s): **Claims 26 - 44** each refer to "Scheme 2" or "Scheme 3" in the Specification, but neither Scheme is recited in the claims.